Efficacy and safety of vamorolone during 48-week treatment in patients with Duchenne Muscular Dystrophy (DMD) in the VBP15-004 study

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Background

- Vamorolone is a dissociative steroidal anti-inflammatory drug that seeks to retain efficacy and reduce safety concerns in patients with Duchenne muscular dystrophy (DMD) compared to corticosteroids via changes to structure/activity relationships with the glucocorticoid receptor.[1]
- A series of open-label studies (VBP15-LTE, NCT03038399) in boys with DMD suggested a favorable efficacy–safety profile over 30 months of exposure.[2]
- The efficacy and safety of vamorolone were investigated during the first 24-weeks (Period 1) of the VISION-DMD (VBP15-004, NCT03439670) study:
  - The results of the primary analysis at 24 weeks have been reported previously.[3]
  - The study met its primary endpoint; both doses of vamorolone (6 mg/kg/day and 2 mg/kg/day) showed statistically significant and clinically meaningful improvement in functional outcomes vs. placebo after 24 weeks of treatment.

Objectives

- The objective of this analysis was to evaluate the efficacy and safety of continuous 48-week vamorolone treatment.

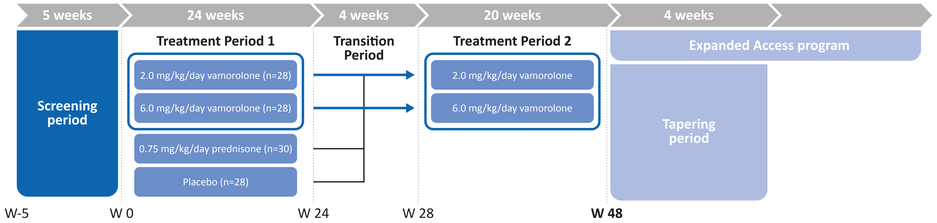
Methods

- VISION-DMD (VBP15-004) is a 48-week randomized, double-blind study comprising two periods.
  - During Period 1, 121 patients were randomized 1:1:1:1 to vamorolone 2 or 6 mg/kg/day, prednisone 0.75 mg/kg/day, or placebo for 24 weeks.
  - During Period 2, patients continued their initial vamorolone dose or crossed over from placebo or prednisone to vamorolone 2 or 6 mg/kg/day.
- The patients were 4–<7 years of age at baseline with centrally confirmed DMD who could walk independently without assistive devices and complete the time to stand from supine (TTSTAND) test without assistance in <10 seconds at baseline. The patients were steroid-naïve at baseline.
- The analysis is conducted in patients who were randomized to receive vamorolone 2 or 6 mg/kg/day throughout the 48-week study, modified intention to treat-2 population **(Figure 1)**. The patients who did not participate in Treatment Period 2 were excluded from this analysis.
- Global efficacy was assessed as change from baseline to week 48 in TTSTAND velocity, 6-minute walk distance (6MWT), Time to run/walk 10 m (TTRW) velocity, North Star Ambulatory Assessment (NSAA) score, Time to climb 4 steps (TTCLIMB) velocity and was modelled using restricted maximum likelihood-based mixed model for repeated measures (MMRM).

Results

- Of the 121 patients randomized to the study, 56 received vamorolone during Periods 1 and 2.
  - Two of 56 patients discontinued treatment during Period 2 (1 adverse event [AE], 1 consent withdrawn).

Figure 1. Study design for VISION-DMD (VBP15-004).



This poster focuses on analysis of patients who received either vamorolone 2 mg/kg/day or vamorolone 6 mg/kg/day in Period 1 and continued on vamorolone in Period 2.

Summary

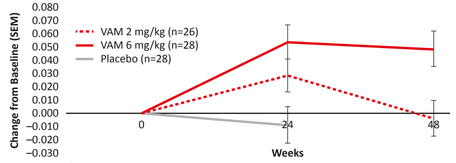
- Baseline characteristics were similar across groups for age and most functional outcomes **(Table 1)**. As indicated by the percentiles, the patients were shorter and had a higher BMI than the average of their age-matched general population.
- In TTSTAND velocity, the effect seen at Week 24 for vamorolone 6 mg/kg/day was maintained until Week 48, with a significant difference vs. vamorolone 2 mg/kg/day at Week 48 (p=0.001) **(Figure 2)**.
- In the other endpoints, differences between dose levels were seen in 6MWT (p=0.047) and TTCLIMB (p=0.031), while not in TTRW (p=0.375) or NSAA (p=0.602) **(Figure 3)**.
- Three serious AEs were reported during the 48 weeks: perforated appendicitis (6 mg/kg/day), asthma (6 mg/kg/day), and viral gastroenteritis (2 mg/kg/day), all considered unrelated to vamorolone.
- The most common AEs reported during the 48-week vamorolone treatment were:
  - Upper respiratory tract infections (vamorolone 2 mg/kg/day: 35.7% [n=10]; vamorolone 6 mg/kg/day: 14.3% [n=4])
  - Vomiting (vamorolone 2 mg/kg/day: 21.4% [n=6]; vamorolone 6 mg/kg/day: 21.4% [n=6])
  - Cushingoid features (vamorolone 2 mg/kg/day: 14.3% [n=4]; vamorolone 6 mg/kg/day: 32.1% [n=9])
  - Cough (vamorolone 2 mg/kg/day: 17.9% [n=5]; vamorolone 6 mg/kg/day: 10.7% [n=3])
  - Pyrexia (vamorolone 2 mg/kg/day: 25.0% [n=7]; vamorolone 6 mg/kg/day: 10.7% [n=3])
  - Diarrhoea (vamorolone 2 mg/kg/day: 10.7% [n=3]; vamorolone 6 mg/kg/day: 17.5% [n=5])
- There was no increase in rates of adverse events from Period 1 to Period 2 for any of the vamorolone doses **(Figure 4)**.
- No stunting of growth was observed with either vamorolone dose.
  - The average baseline height indicated a height lower than in the general age-matched population in keeping with known natural history **(Table 1)**.
  - Mean (SD) change from baseline to week 48 for vamorolone 2 and 6 mg/kg/day was 0.13 (0.277) and 0.29 (0.355) **(Figure 5)** in contrast to stunting of growth known to occur with corticosteroids.[4]
  - In a separate analysis, growth trajectory was preserved with vamorolone in Period 2 following treatment with prednisone during Period 1.[5]
- Body mass index (BMI) stabilized for the vamorolone 6 mg/kg/day group in Period 2 after an initial increase observed during the first 24 weeks **(Figure 6)**.

Table 1. Characteristics at baseline (study entry), mITT-2 / Safety-2 population

	Continuous vamorolone 2 mg/kg/day (n=28) Mean (SD)	Continuous vamorolone 6mg/kg/day (n=28) Mean (SD)
Age (years)	5.3 (0.9)	5.4 (0.9)
TTSTAND (sec)	6.0 (2.4)	6.0 (2.0)
6-MWT (m)	317 (60)	313 (56)
NSAA (points)	17.5 (4.6)	18.9 (4.1)
Height (percentile)	32.0 (29.2)	23.2 (24.6)
Weight (percentile)	43.1 (29.0)	43.7 (26.7)
BMI (percentile)	63.5 (27.9)	69.8 (23.0)

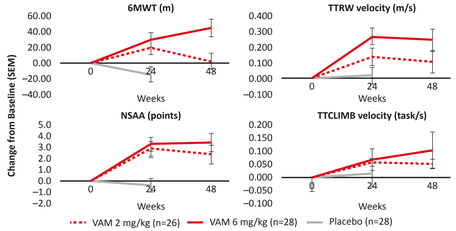
6MWD, six-minute walk distance; BMI, body mass index; mITT-2, modified intention to treat-2 population; TTSTAND, time to stand from supine; NSAA, North Star Ambulatory Assessment; SD, standard deviation.

Figure 2. TTSTAND velocity (rises/sec) (mITT-2 population, MMRM)



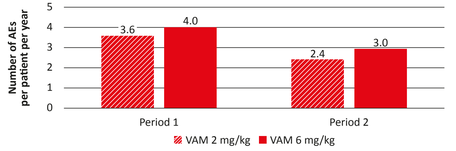
mITT-2, modified intention to treat-2 population; MMRM, mixed model for repeated measures; SEM, standard error of the mean; TTSTAND, time to stand from supine; VAM, vamorolone.

Figure 3. 6MWT distance (m), TTRW velocity (m/sec), NSAA score (points) and TTCLIMB velocity (tasks/s) (mITT-2 population, MMRM)



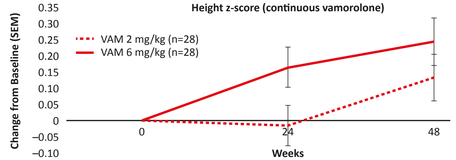
6MWD, six-minute walk distance; mITT-2, modified intention to treat-2 population; MMRM, mixed model for repeated measures; TTCLIMB, time to climb 4 steps; TTRW, time to run/walk 10 m; NSAA, North Star Ambulatory Assessment; SEM, standard error of the mean; VAM, vamorolone.

Figure 4. Rates of Adverse Events reported by Period



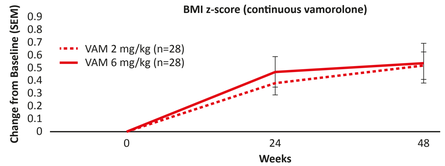
AE, adverse event; VAM, vamorolone.

Figure 5. Change in height z-score (Safety-2 population, MMRM)



MMRM, mixed model for repeated measures; SEM, standard error of the mean; VAM, vamorolone.

Figure 6. Change in BMI z-score (Safety-2 population, MMRM)



BMI, body mass index; MMRM, mixed model for repeated measures; SEM, standard error of the mean; VAM, vamorolone.

Conclusions

- Efficacy of vamorolone 6 mg/kg/day established at 24 weeks was maintained over 48 weeks across all outcome measures, while only across some measures for 2 mg/kg/day.
- Vamorolone treatment was generally well tolerated at both dose levels throughout 48 weeks.
- For subjects who continued on the same dose of vamorolone throughout the study, the safety profile was consistent at week 48 compared to the results previously reported at week 24.
- No stunting of growth was seen with either vamorolone dose, consistent with data previously presented from long-term open-label studies.
- BMI z-score stabilized in Period 2.
- The longer-term results of the VISION-DMD (VBP15-004) study confirm earlier findings regarding the efficacy with a differentiated safety profile and no stunting of growth.

References

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